3/23/98

08/817595

L10 20 L5 AND (IMMUNE RESPONSE)

=> dup rem l10

PROCESSING COMPLETED FOR L10
L11 11 DUP REM L10 (9 DUPLICATES REMOVED)

=> d l11 1-11 bib ab

L11 ANSWER 1 OF 11 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
AN 95250176 EMBASE
TI Modulation by canine interferon-.gamma. of major histocompatibility complex and tumor-associated antigen expression in canine mammary tumor and melanoma cell lines.
AU Whitley E.M.; Church Bird A.; Zucker K.E.; Wolfe L.G.
CS Department of Pathobiology, College of Veterinary Medicine, Auburn University, Auburn, AL 36849-5519, United States
SO Anticancer Research, (1995) 15/3 (923-929).
ISSN: 0250-7005 CODEN: ANTRD4
CY Greece
DT Journal
FS 016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB In an effort to enhance the antigenicity of canine tumor cells, canine interferon-gamma (CnIFN-.gamma.) was applied in vitro to seven mammary tumor (CMT) and two canine melanoma (CML) cell lines. Surface expression of major histocompatibility complex (**MHC**) **antigens** and tumor-associated antigens (TAA) was measured by a flow cytometric fluorescence assay using commercially available anti-MHC antibodies, and anti-canine TAA monoclonal antibodies generated against CMT and CML cell lines. Compared to constitutive antigen levels in untreated cells, **treatment** with CnIFN-.gamma. resulted in increased expression of MHC class I and II antigens (up to 19- and 167-fold, respectively) and a TAA (up to 5-fold) by CMT cell lines, and increased expression of class I antigen (131-fold) by one CML and of class II antigen (18-fold) by the other CML cell line. Expression of **MHC** **antigens** and a TAA by tumor cells was increased by Cn-IFN-.gamma. **treatment**, and such an increase may be of potential benefit in tumor cell recognition and rejection by the immune system.

L11 ANSWER 2 OF 11 MEDLINE DUPLICATE 1
AN 95245500 MEDLINE
DN 95245500
TI Human class II major histocompatibility complex gene transfer into murine neuroblastoma leads to loss of tumorigenicity, immunity against subsequent tumor challenge, and elimination of microscopic preestablished tumors.

AU Hock R A; Reynolds B D; Tucker-McClung C L; Kwok W W
CS Herman B. Wells Center for Pediatric Research, Riley Hospital for Children, Indianapolis, IN 46202-5225, USA.
NC PO1-CA59348 (NCI)
SO JOURNAL OF IMMUNOTHERAPY WITH EMPHASIS ON TUMOR IMMUNOLOGY, (1995 Jah) 17 (1) 12-8.
Journal code: BZH. ISSN: 1067-5582.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199508
AB Immunological recognition of transformed cells is critically important to limit tumor development and proliferation. Because established tumors have escaped immune recognition and elimination, novel strategies to enhance antitumor immunity have been developed. A unique approach has used the introduction of genes encoding major histocompatibility complex (**MHC**) **antigens** into tumor cells. Experiments in mice have shown that the expression of syngeneic class II **MHC antigens** in tumor cells completely abrogates tumorigenicity and induces tumor-specific immunity. In this study we sought to determine whether a more effective antitumor **immune response** would be generated by introducing xenogeneic class II MHC genes into tumor cells. To address this question we used recombinant retroviruses to express human class II MHC genes in a highly malignant murine neuroblastoma cell line, Neuro-2a. We found that normal mice inoculated with Neuro-2a expressing the human class II MHC antigen did not develop tumors and were immune to subsequent challenge with unmodified Neuro-2a cells. In addition, mice bearing small established Neuro-2a tumors were cured by vaccination with Neuro-2a expressing human class II MHC. We hypothesize that a similar approach using retroviral-mediated transduction of class II MHC genes into human tumor cells may be an effective alternative to current **cancer treatment**.

after the Applicant's invention (priority to 94)

L11 ANSWER 3 OF 11 MEDLINE DUPLICATE 2
AN 95012404 MEDLINE
DN 95012404
TI Human hepatoma cells expressing **MHC antigens** display accessory cell function: dependence on LFA-1/ICAM-1 interaction.
AU Paroli M; Carloni G; Franco A; De Petrillo G; Alfani E; Perrone A; Barnaba V
CS Fondazione Andrea Cesalpino, I Clinica Medica, Universit`a La Sapienza, Roma, Italy.
SO IMMUNOLOGY, (1994 Jun) 82 (2) 215-21.
Journal code: GH7. ISSN: 0019-2805.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199501
AB Malignant transformation of human hepatocytes is often accompanied by an increased expression of major histocompatibility complex (MHC) molecules, but whether this phenomenon is related to an enhanced immunogenicity remains unknown. In this study, we tested the capacity of a series of human hepatoma cell lines to induce proliferation of allogeneic T cells in primary mixed lymphocyte **tumour** cultures (MLTC). These cell lines were positive for class I molecules, whereas class II molecule expression was either constitutive or inducible by **treatment** with interferon-gamma (IFN-gamma). We found that HA22T/VGH cells

expressing class II molecules constitutively stimulated high proliferative responses of purified CD4+ T lymphocytes, whereas class II-negative Li7A cells stimulated CD4+ T-cell responses only when induced by **treatment** with IFN-gamma. HA22T/VGH and Li7A cells also exerted a significant stimulatory activity for purified CD8+ T cells whereas HepG2 cells, in which MHC class II molecules are neither constitutive IFN-gamma-inducible, were unable to induce CD4+ and CD8+ T-cell proliferative responses. Phenotypical analysis revealed that HA22T/VGH and Li7A expressed high levels of intracellular adhesion molecule-1 (ICAM-1) and experiments with blocking monoclonal antibodies (mAb) demonstrated that this molecule played a key role in mediating the co-stimulatory function of hepatoma cells. In addition, HA22T/VGH cells were found to produce mRNA for interleukin-1 (IL-1) beta and IL-6, while Li7a only produced IL-1 beta, yet both these cytokines were found to play a small part, if any, in T-cell co-activation. On the whole, these results show tht hepatoma cells expression **MHC antigens** and ICAM-1 are able to deliver signals necessary for activation of resting CD4+ and CD8+ T cells and suggest that they may actively participate in the anti-**tumour immune response**.

L11 ANSWER 4 OF 11 CANCERLIT
AN 92684535 CANCERLIT
DN 92684535
TI REGRESSION OF SKIN RECURRENCES OF BREAST CARCINOMAS **TREATED** WITH INTRALESIONAL INJECTIONS OF INTERFERONS (MEETING ABSTRACT).
AU Ozzello L; Habif D V; DeRosa C M; Cantell K
CS Columbia Univ., New York, NY 10032.
SO Proc Annu Meet Am Assoc Cancer Res, (1992). Vol. 33, pp. A2002. ISSN: 0197-016X.
DT (MEETING ABSTRACT)
FS ICDB
LA English
EM 199209
AB Skin recurrences of breast carcinomas were **treated** with 10 intralesional injections of natural interferon (nIFN) alpha (3x10(6) IU) and gamma (1x10(6) IU). Complete regressions occurred in 5/11 lesions **treated** with nIFN alpha and in 5/7 **treated** with nIFN alpha/nIFN gamma. Of the remaining 8 lesions, 7 underwent partial regression, and 1 (nIFN alpha) showed no response. In 6 instances, multiple recurrences were injected simultaneously and were excised at fixed intervals during and after therapy. Salient immunohistochemical findings in responding lesions included inhibition of mitotic activity and upregulation of antigenic expression (epithelial membrane antigen, HLA-DR, HLA-A,B,C and ICAM-1) by the **cancer** cells; activation of macrophages and dendrocytes with marked expression of **MHC antigens** ; recruitment and activation of CD3+ T lymphocytes, many of which coexpressed CD4/CD8; and activation of endothelium with enhancement of antigenic expression, procoagulant activity and vascular permeability. The above responses were greater with nIFN alpha/nIFN gamma. It was concluded that the IFNs affected the carcinoma cells through an antiproliferative action and by stimulating a cell-mediated **immune response**.

L11 ANSWER 5 OF 11 SCISEARCH COPYRIGHT 1998 ISI (R)
AN 92:327926 SCISEARCH
GA The Genuine Article (R) Number: HV676
TI A NONIMMUNOGENIC SARCOMA TRANSDUCED WITH THE CDNA FOR INTERFERON-GAMMA ELICITS CD8+ T-CELLS AGAINST THE WILD-TYPE TUMOR - CORRELATION WITH ANTIGEN PRESENTATION CAPABILITY
AU RESTIFO N P (Reprint); SPIESS P J; KARP S E; MULE J J; ROSENBERG S A

CS NCI, DIV CANC TREATMENT, SURG BRANCH, BETHESDA, MD, 20892 (Reprint)
CYA USA
SO JOURNAL OF EXPERIMENTAL MEDICINE, (01 JUN 1992) Vol. 175, No. 6, pp. 1423-1431.
ISSN: 0022-1007.
DT Article; Journal
FS LIFE
LA ENGLISH
REC Reference Count: 48
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB To be recognized by CD8+ T lymphocytes, target cells must process and present peptide antigens in the context of major histocompatibility complex (MHC) class I molecules. The nonimmunogenic, low class I-expressing, methylcholanthrene (MCA)-induced murine sarcoma cell line, MCA 101, is a poor presenter of endogenously generated viral antigens to specific CD8+ T lymphocytes and cannot be used to generate tumor infiltrating lymphocytes (TIL). Since interferon-gamma (IFN-gamma) has been shown to upregulate three sets of molecules important for antigen processing and presentation, we retrovirally transduced wild-type MCA 101 (101.WT) tumor with the mIFN-gamma-cDNA to create the 101.NAT cell line. Unlike 101.WT, some clones of retrovirally transduced 101.NAT tumor expressed high levels of class I, and could be used to generate CD8+ TIL. More importantly, these TIL were therapeutic in vivo against established pulmonary metastases from the wild-type tumor. Although not uniformly cytotoxic amongst several separate cultures, these TIL did specifically release cytokines (IFN-gamma and tumor necrosis factor-alpha) in response to 101.WT targets. 101.WT's antigen presentation deficit was also reversed by gene modification with mIFN-gamma-cDNA. 101.NAT had a greatly improved capacity to present viral antigens to CD8+ cytotoxic T lymphocytes. These findings show that a nonimmunogenic tumor, incapable of generating a CD8+ T cell **immune response**, could be gene-modified to generate a therapeutically useful **immune response** against the wild-type tumor. This strategy may be useful in developing **treatments** for tumor histologies not thought to be susceptible to T cell-based immunotherapy.

L11 ANSWER 6 OF 11 CANCERLIT
AN 92680108 CANCERLIT
DN 92680108
TI EFFECT OF LOCAL INJECTION OF INTERFERON GAMMA ON CELL-MEDIATED IMMUNITY OF PATIENTS WITH UTERINE CERVICAL CARCINOMAS.
AU Honma S; Nakamura M; Maruhashi T; Kanazawa K; Takahashi T; Sasagawa S; Tanaka K
CS Dept. of Obstetrics and Gynecology, Niigata Univ. Sch. of Medicine, Niigata, Japan.
SO Serono Symp Publ Raven Press, (1991). Vol. 82, pp. 227-36.
DT Book; (MONOGRAPH)
FS ICDB
LA English
EM 199204
AB Major histocompatibility complex (MHC) class I antigens are expressed on virtually every nucleated cell and play an essential role in **immune response**. In contrast, class II antigens show more restricted distribution, chiefly on the surfaces of immunocompetent cells, including monocytes/macrophages, B lymphocytes, and activated T lymphocytes. To analyze how the generation of cell-mediated **immune response** depends on the degree of differentiation of uterine cervical **cancer** cells, the tumor-infiltrating lymphocytes in association with **MHC antigens** on tumor cells

were studied immunohistochemically. To investigate the mechanisms by which interferon (IFN) exerts its biologic effects in vivo, induction and augmentation of MHC antigen expression on **cancer** cells and recruitment of immune cells were analyzed in **cancer** tissues **treated** by perilesional injection of IFN-gamma (2 x 10[6] units/day x 3 days before surgery). Samples of tumor tissue were collected from cervical lesions immediately following radical hysterectomy in 45 patients ranging in age from 32 to 84 yr. Neither significant induction nor enhancement of immunohistochemical staining for human leukocyte group A antigen expression on **cancer** cells and subsequent infiltration of immune cells has been demonstrated in contrast to previously reported in vitro results. Factors such as dose levels, duration of **treatment**, and genetic makeup of the recipient may be behind these differences. Hysterectomy was performed three days after IFN injection and hypertrophic response was noted in pelvic lymph nodes in most patients, although no significant reduction in tumor size was observed in the primary cervical lesions. With the present data, the in vivo efficacy of IFN cannot be evaluated with respect to inhibition of **cancer** cell growth, but changes in immune cells suggest that this local injection would most likely function as antitumor **treatment** by activating immune cells. (11 Refs)

L11 ANSWER 7 OF 11 SCISEARCH COPYRIGHT 1998 ISI (R)
AN 91:327329 SCISEARCH
GA The Genuine Article (R) Number: FP287
TI CAPACITY OF CD8+ T-CELLS TO REJECT IMMUNOGENIC VARIANTS OF A SPONTANEOUS MURINE CARCINOMA - LACK OF NONSPECIFIC (NK1.1+) EFFECTOR MECHANISMS
AU ELLIOTT B E (Reprint); BARRON A; MAXWELL L; CARLOW D A; MACNAUGHTON S; PROSS H
CS QUEENS UNIV, DEPT PATHOL, CANC RES LABS, KINGSTON K7L 3NG, ONTARIO, CANADA (Reprint); QUEENS UNIV, DEPT MICROBIOL & IMMUNOL, KINGSTON KL7 3NG, ONTARIO, CANADA
CYA CANADA
SO SCANDINAVIAN JOURNAL OF IMMUNOLOGY, (1991) Vol. 33, No. 6, pp. 683-690.
DT Article; Journal
FS LIFE
LA ENGLISH
REC Reference Count: 32
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Class I MHC-expressing (Ia-) immunogenic (imm+) variants, which elicit a strong syngeneic host immune rejection response, can be isolated following 5-azacytidine **treatment** from the MHC-negative non-immunogenic (imm-) murine carcinoma cell line SP1 (10.1 subclone). In the present study, we have shown that CD4-depleted CD8+ T cells are both necessary and sufficient for the rejection process. **Treatment** of semi-syngeneic B6 x CBA F1 mice with anti-NK1.1 antibodies had no effect on the rejection of immunogenic variants, although the splenic NK (natural killer) activity of recipients was fully abrogated. Thus NK 1.1+ effectors, which include most NK and LAK (lymphokine activated killer) cells, are most likely not involved in the rejection process. This finding was supported by a complete lack of NK susceptibility of SP1 cells in vitro, although variable killing by LAK and poly-I:C-induced killer cells was observed. To assess the role of NK1.1- LAK and other non-T killers (e.g. cytolytic macrophages) in vivo, we determined the specificity of the rejection process. We examined the ability of immune animals to reject a mixture of non-immunogenic parent **tumour** cells (or cells of an unrelated syngeneic **tumour**) and of the variant **tumour** cells used for

the initial immunization. Growth of the parent **tumour** cells was unaffected while the same animals rejected the immunogenic **tumour** cells. Our findings support a primary role of **tumour**-specific CD8+ T cells in the rejection of imm+ variants with no detectable involvement of non-specific effector cells in the **tumour** destruction process.

L11 ANSWER 8 OF 11 MEDLINE DUPLICATE 3
AN 91013447 MEDLINE
DN 91013447
TI Major histocompatibility complex class II antigens on renal cell **cancer**--immunohistochemical study and effect on their expression by interferon.
AU Tomita Y
CS Department of Urology, Niigata University School of Medicine.
SO NIPPON HINYOKIKA GAKKAI ZASSHI. JAPANESE JOURNAL OF UROLOGY, (1990 Jul) 81 (7) 1079-86.
Journal code: KRB. ISSN: 0021-5287.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
EM 199101
AB Products of major histocompatibility complex (MHC) play important roles in immune reaction. Class II **MHC antigens** serve as restriction elements for cells presenting antigens to CD4-positive helper T cells and also as histocompatibility antigens responsible for graft rejection. Furthermore, it was reported that expression of class II antigens on tumor cells increases immunogenicity in the murine system. In an attempt to investigate the relationship between renal cell **cancer** (RCC) and host's immune responses, we examined the expression of class II **MHC antigens** on RCC tissues of 30 cases and tumor cell lines. Immunohistochemical study showed that class II antigens were detected on 29 out of 30 RCC tissues to various degrees with an order of positivity DR greater than DP greater than DQ but not normal renal tubular cells. Significant correlation was found between the expression of DQ or DP and the degree of lymphocyte infiltration. Three lines of RCC were examined by flowcytometric analysis, and were found to lack class II antigens. In KRC/Y and ACHN, however, HLA-DR-positive cells and in KRC/Y a smaller number of HLA-DP-positive cells were found when these cells were **treated** with interferon-gamma but not interferon-alpha. The result suggests that the expression of class II antigens on RCC might be modified by interferon-gamma which is produced by tumor infiltrating lymphocytes or administrated for **cancer treatment**. Their expression is considered to affect host's **immune response** to RCC.

L11 ANSWER 9 OF 11 MEDLINE DUPLICATE 4
AN 90170035 MEDLINE
DN 90170035
TI MHC class II antigen expression in human vascular smooth muscle cells is induced by interferon-gamma and modulated by **tumour** necrosis factor and lymphotoxin.
AU Stemme S; Fager G; Hansson G K
CS Department of Clinical Chemistry, Gothenburg University, Sweden..
SO IMMUNOLOGY, (1990 Feb) 69 (2) 243-9.
Journal code: GH7. ISSN: 0019-2805.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199006

AB Arterial smooth muscle cells (SMC) express major histocompatibility complex (MHC) class II antigens in experimental vasculitis and in the human atherosclerotic plaque. We have therefore studied the regulation of expression of **MHC antigens** in cultured human arterial SMC, using immunofluorescence, radioimmunoprecipitation and a quantitative cell-surface immunoradiometric assay. SMC expressed class I, but not class II, antigens on their cell surfaces under basal conditions. **Treatment** of SMC with recombinant or natural interferon-gamma (IFN-gamma) induced expression of class II antigens in the following order of intensity, DR greater than DP greater than DQ. HLA-DR protein in SMC showed the same MW as that synthesized by B-lymphoblastoid cells. Antibodies to IFN-gamma blocked all HLA-DR-inducing activity in mixed leucocyte reaction (MLR) supernatants and PHA-stimulated peripheral blood mononuclear cell (PBMC)-conditioned media, indicating that IFN-gamma is the only lymphokine secreted under these conditions that is capable of de novo induction of HLA-DR expression in SMC. **Treatment** of SMC with recombinant human **tumour** necrosis factor-alpha (TNF) or lymphotoxin (LT) did not per se induce class II antigen expression. However, both TNF and LT substantially enhanced IFN-gamma-induced expression of HLA-DQ while decreasing that of HLA-DP. TNF, but not LT, increased HLA-DR expression. Also, in dermal fibroblasts, IFN-gamma-induced HLA-DP expression was significantly inhibited in the presence of TNF. These data demonstrate that TNF and LT differentially modulate IFN-gamma-induced MHC antigen expression in mesenchymal cells. The fact that SMC can express MHC class II antigens suggests that this cell type may serve as an accessory cell in the initiation of the **immune response**.

L11 ANSWER 10 OF 11 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
AN 86168262 EMBASE
TI Phase II study of vaccinia melanoma cell lysates (VMCL) as adjuvant to surgical **treatment** of stage II melanoma. II. Effects on cell mediated cytotoxicity and leucocyte dependent antibody activity: Immunological effects of VMCL in melanoma patients.
AU Hersey P.; Edwards A.; D'Alessandro G.; MacDonald M.
CS Oncology and Immunology Unit, Royal Newcastle Hospital, Newcastle, NSW 2300, Australia
SO CANCER IMMUNOL. IMMUNOTHER., (1986) 22/3 (221-231).
CODEN: CIIMDN
CY Germany, Federal Republic of
LA English
AB Patients with stage II melanoma were vaccinated with vaccinia virus-induced melanoma cell lysates (VMCL). The vaccine contained viable vaccinia virus, membranous fragments and no intact nuclei. A number of antigens defined by monoclonal antibodies were detected in the vaccine including the ganglioside GD3 and DR antigens. Administration of the vaccine was associated with depression of natural killer cell activity against melanoma and K562 target cells in the first 3-6 months of **treatment**. Leucocyte dependent antibody (LDA) activity against melanoma cells was induced or increased in titre in approximately half of the patient studied. Continued vaccination was associated in a number of patients with a decreased LDA titres. Studies on a small samples of patients revealed that this was associated with the development of serum factors which inhibited LDA activity. LDA activity appeared directed to non-**MHC antigens** on melanoma cells which were of at least two specificities. One specificity which was shared with antigens on a number of nonmelanoma carcinoma cells was removed by absorption on fetal brain and may be similar to oncofetal antigens described by other workers. Reactivity against melanocytes was

induced in some patients and may underlie the development of vitiligo in several patients. These results suggest that vaccines prepared from VMCL may be a favourable method for increasing immune responses against melanoma.

L11 ANSWER 11 OF 11 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
AN 83080184 EMBASE
TI Studies of allogeneic tumor transplants: Induced rejection of advanced tumors by immune alteration of recipients.
AU Russell P.S.; Chase C.M.; Burton R.C.
CS Transplant. Unit, Dep. Surg., Harvard Med. Sch., Massachusetts Gen. Hosp., Boston, MA, United States
SO J. IMMUNOL., (1983) 130/2 (951-957).
CODEN: JOIMA3
CY United States
LA English
AB In the present experiments, a methylcholanthrene-induced sarcoma (S-702) of B10.D2 origin was found to grow rapidly in B6AF1 mice leading to the death of all recipients in 5 to 9 wk. Nevertheless, immunity to **MHC antigens** presented by the tumor was readily demonstrable in tumor-bearing mice by their responses to donor strain skin grafts until late in the course of tumor growth, when a nonspecific form of immune suppression developed. In addition, B6AF1 mice preimmunized by exposure to B10.D2 donor strain antigens did not permit tumor growth. **Treatment** of tumor-bearing B6AF1 mice with CY at 18 days, when the tumors measured over 12-mm in diameter, followed by the i.p. injection of B10.D2 lymphoid cells (at a dosage of from 1.2 to 2.5 X 108 cells) resulted in the complete regression of 100% of these large tumors. CY **treatment** combined with localized immune stimuli in the form of donor strain skin grafts or secondary tumor implants was incapable of producing a sufficiently heightened **immune response** to cause tumor rejection. A dose of CY temporarily retarded tumor growth in most mice, and in a minority of animals so **treated** (<25%) tumors regressed completely. In syngeneic (B10.D2) animals, CY also temporarily slowed tumor growth, but total regression was never observed. An effective B10.D2 cell inoculum could consist not only of living lymphoid cells but of irradiated (1000 rad) cells as well. Tumor cell suspensions (after irradiation, 10,000 rad) were also effective. These observations suggest local immune factors at the host-tumor interface may have been of importance in the survival of these allogeneic tumor transplants and that CY influenced this state, perhaps through an influence on suppressor cells, allowing subsequent administration of donor strain

=> s MHC antigen!

L1 4371 MHC ANTIGEN!

=> s vaccin? and l1

L2 86 VACCIN? AND L1

=> s l2 and (tumo!r or cancer)

L3 13 L2 AND (TUMO!R OR CANCER)

=> dup rem l3

PROCESSING COMPLETED FOR L3
L4 5 DUP REM L3 (8 DUPLICATES REMOVED)

=> d l4 1-5 bib ab

L4 ANSWER 1 OF 5 MEDLINE DUPLICATE 1
AN 97164642 MEDLINE
DN 97164642
TI Eradication of melanoma pulmonary metastases by immunotherapy with tumor cells engineered to secrete interleukin-2 or gamma interferon.
AU Abdel-Wahab Z; Dar M; Osanto S; Fong T; Vervaert C E; Hester D; Jolly D; Seigler H F
CS Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710, USA.
NC RO1-CA-64959 (NCI)
SO CANCER GENE THERAPY, (1997 Jan-Feb) 4 (1) 33-41.
Journal code: CE3. ISSN: 0929-1903.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199706
EW 19970603
AB This study was undertaken to investigate the effectiveness of interleukin-2 (IL-2) and gamma interferon (gammaIFN)-modified B16 melanoma cells in the immunotherapy of established melanoma pulmonary metastases. The genes for IL-2 and gammaIFN were introduced retrovirally into B16 melanoma cells. Transduction with the gammaIFN, but not the IL-2, gene caused significant increases in the expression of major histocompatibility complex (**MHC**) **antigens** on B16-gammaIFN cells. The in vivo tumor-forming capacity of both IL-2- and gammaIFN-transduced B16 cells was drastically reduced when the cells were inoculated subcutaneously (SC) in syngeneic C57BL/6 mice. After intravenous (IV) inoculation, most of the B16-gammaIFN cells were rejected, but B16-IL-2 cells were relatively tumorigenic and formed pulmonary metastases. C57BL/6 mice bearing 4-day established parental B16 lung metastases were treated with B16 parental (B16P) unmodified cells, IL-2- or gammaIFN-modified B16 cells, or a combination of both transduced

cells. Treatment consisted of a weekly intraperitoneal (IP) injection of one million irradiated (10,000 rad) tumor cells alone or in combination with exogenous IL-2 for a total of three to four injections. Immunotherapy with B16 parental or B16-IL-2 secreting cells caused a moderate reduction in the number of lung metastases. However, mice treated with gammaIFN-secreting B16 cells showed a significant reduction or complete elimination of lung metastases. There was no additive effect for combining both IL-2- and gammaIFN-modified tumor cells in the immunotherapy. Exogenous IL-2 (50,000-100,000 U/day for 3 days) caused a significant enhancement of the immunotherapeutic benefit of the **vaccines**. Moreover, mice treated with gammaIFN-modified B16 cells survived longer than the other groups. Twenty-five percent of these mice were tumor free and remained alive for an observation period of 4 months. The in vitro cytolytic activity of splenocytes in chromium release assays did not correlate in every case with the in vivo antitumor effect of the treatment. Our findings have implications for the use of cytokine-modified cells for immunotherapy and for evaluating the therapeutic benefit of this novel treatment.

L4 ANSWER 2 OF 5 MEDLINE DUPLICATE 2
AN 96400418 MEDLINE
DN 96400418
TI Effect of irradiation on cytokine production, MHC antigen expression, and **vaccine** potential of interleukin-2 and interferon-gamma gene-modified melanoma cells.
AU Abdel-Wahab Z; Dar M M; Hester D; Vervaert C; Gangavalli R; Barber J; Darrow T L; Seigler H F
CS Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710, USA.
NC RO1-CA-64959-01 (NCI)
SO CELLULAR IMMUNOLOGY, (1996 Aug 1) 171 (2) 246-54.
Journal code: CQ9. ISSN: 0008-8749.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199701
EW 19970104
AB Recent studies have shown that tumor cells transduced with interleukin-2 (IL-2) or interferon-gamma (IFN-gamma) genes stimulated a potent and specific antitumor immunity in experimental animals. For use as a human **vaccine**, tumor cells must be inactivated by irradiation to ensure the arrest of their growth. This study was undertaken to examine the effects of irradiation (10,000 rad) on the growth characteristics and **vaccine** potential of IL-2 and IFN-gamma-modified human melanomas and B16 murine melanoma. Irradiation caused cessation of cell growth and gradual reduction of cell number. Irradiated melanoma cells displayed 1.5 to 10-fold increases in the surface expression of MHC class I and/or class II antigens. The increases in **MHC antigens** persisted for 7-14 days postirradiation and then declined thereafter. Furthermore, IL-2- and IFN-gamma-transduced melanoma cells showed enhanced expression of the cytokine mRNA and increased cytokine secretion after irradiation. The effect of irradiation on the **vaccine** potential of the transduced cells was examined in C57BL/ 6 mice by prophylactic immunization and immunotherapy, and in nude mice by mixed transplantation assays. The irradiated, cytokine-transduced B16 cell **vaccine** was as or more effective than the unirradiated **vaccine**. These irradiated **vaccines** protected the animals against a challenging tumorigenic dose of B16 parental cells and suppressed the growth of 4-day-established B16 lung metastases. The ability of

the irradiated IL-2-transduced human melanomas to inhibit the growth of admixed parental melanoma cells was retained but was less efficacious than unirradiated cells. The results suggest that irradiation does not abrogate the **vaccine** potential of IL-2- and IFN-gamma-transduced melanomas. These findings have implications for designing specific active immunotherapy protocols utilizing cytokine gene-modified tumor cells.

L4 ANSWER 3 OF 5 MEDLINE DUPLICATE 3
AN 95245500 MEDLINE
DN 95245500
TI Human class II major histocompatibility complex gene transfer into murine neuroblastoma leads to loss of tumorigenicity, immunity against subsequent tumor challenge, and elimination of microscopic preestablished tumors.
AU Hock R A; Reynolds B D; Tucker-McClung C L; Kwok W W
CS Herman B. Wells Center for Pediatric Research, Riley Hospital for Children, Indianapolis, IN 46202-5225, USA.
NC PO1-CA59348 (NCI)
SO JOURNAL OF IMMUNOTHERAPY WITH EMPHASIS ON TUMOR IMMUNOLOGY, (1995 Jan) 17 (1) 12-8.
Journal code: BZH. ISSN: 1067-5582.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199508
AB Immunological recognition of transformed cells is critically important to limit tumor development and proliferation. Because established tumors have escaped immune recognition and elimination, novel strategies to enhance antitumor immunity have been developed. A unique approach has used the introduction of genes encoding major histocompatibility complex (**MHC**) **antigens** into tumor cells. Experiments in mice have shown that the expression of syngeneic class II **MHC antigens** in tumor cells completely abrogates tumorigenicity and induces tumor-specific immunity. In this study we sought to determine whether a more effective antitumor immune response would be generated by introducing xenogeneic class II MHC genes into tumor cells. To address this question we used recombinant retroviruses to express human class II MHC genes in a highly malignant murine neuroblastoma cell line, Neuro-2a. We found that normal mice inoculated with Neuro-2a expressing the human class II MHC antigen did not develop tumors and were immune to subsequent challenge with unmodified Neuro-2a cells. In addition, mice bearing small established Neuro-2a tumors were cured by **vaccination** with Neuro-2a expressing human class II MHC. We hypothesize that a similar approach using retroviral-mediated transduction of class II MHC genes into human tumor cells may be an effective alternative to current **cancer** treatment.

L4 ANSWER 4 OF 5 EMBASE COPYRIGHT 1998 ELSEVIER SCI. B.V.
AN 93278717 EMBASE
TI Active specific immunotherapy of melanoma with allogeneic cell lysates. Rationale, results, and possible mechanisms of action.
AU Mitchell M.S.; Harel W.; Kan-Mitchell J.; LeMay L.G.; Goedegebuure P.; Huang X.-Q.; Hofman F.; Groshen S.
CS Kenneth Norris Jr/, Comprehensive Cancer Center, University of Southern California, Los Angeles, CA 90033, United States
SO ANN. NEW YORK ACAD. SCI., (1993) 690/- (153-166).
ISSN: 0077-8923 CODEN: ANYAA
CY United States
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SL English
AB Since 1985 we have conducted clinical trials with a therapeutic melanoma **vaccine** (melanoma theraccine). Mechanical lysates of two melanoma cell lines chosen for their complementary characteristics were combined with the adjuvant DETOX and injected subcutaneously on weeks 1, 2, 3, 4, and 6 for one or two courses and then monthly in patients with objective clinical responses. Of 106 patients, 20 had objective clinical regression of tumor masses, 5 with complete responses. The median duration of response was 21 months. Twelve patients lived at least 2 years, with a median survival of nearly 3 years. Two of them are free of disease for >2 and >6 years, respectively. However, it was not necessary to achieve complete remissions to cause an increase in survival, and most of the long-surviving patients have one or more (stable) residual nodules. The pace of the disease process was clearly slowed in those individuals. A rise in the level of cytotoxic T-lymphocyte precursors in the blood (pTC) correlated with clinical response. Only those patients who had a rise in pTc had a remission. In addition to 'classical' CD8+ Tc, CD4+ Tc were cloned from the blood of immunized patients. Melanoma-specific Tc of both types that killed autologous melanoma but not matched lymphoblastoid cells were detected. Allogeneic melanoma cell lines were also killed, with mainly HLA-A2/28 and HLA-B12/44/45 degenerate restriction. CD4+ Tc were restricted by HLA Class I antigens, as judged by their killing of HLA Class II-negative melanomas and blocking by anti-class I antibodies. Other CD4+ clones were blocked by both anti-HLA Class I or anti-Class II MHC monoclonal antibodies, and only two were blocked only by anti-HLA Class II. Immunohistology revealed CD4+ and CD8+ T cells in lesions under rejection, but the predominant cells were macrophages, suggesting delayed-type hypersensitivity as a possible mechanism. Clinical responses were found most often in patients with HLA-A2/28, -B12/44/45, and -C3, particuiarly when two or more of those alleles were present. This may have been due either to (1)) similarity of **MHC antigens** between one of the immunizing melanomas and the patient's melanoma or (2) the intrinsic importance of these MHC molecules in presenting melanoma-associated antigens to Tc in vivo. IFN-.alpha.2b salvaged 8 of 18 patients who failed with the theraccine, regardless of MHC phenotype, perhaps through upregulation of MHC and tumor epitopes on the autochthonous tumor.

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AN 86168262 EMBASE
TI Phase II study of **vaccinia** melanoma cell lysates (VMCL) as adjuvant to surgical treatment of stage II melanoma. II. Effects on cell mediated cytotoxicity and leucocyte dependent antibody activity: Immunological effects of VMCL in melanoma patients.
AU Hersey P.; Edwards A.; D'Alessandro G.; MacDonald M.
CS Oncology and Immunology Unit, Royal Newcastle Hospital, Newcastle, NSW 2300, Australia
SO CANCER IMMUNOL. IMMUNOTHER., (1986) 22/3 (221-231).
CODEN: CIIMDN
CY Germany, Federal Republic of
LA English
AB Patients with stage II melanoma were **vaccinated** with **vaccinia** virus-induced melanoma cell lysates (VMCL). The **vaccine** contained viable **vaccinia** virus, membranous fragments and no intact nuclei. A number of antigens

defined by monoclonal antibodies were detected in the **vaccine** including the ganglioside GD3 and DR antigens. Administration of the **vaccine** was associated with depression of natural killer cell activity against melanoma and K562 target cells in the first 3-6 months of treatment. Leucocyte dependent antibody (LDA) activity against melanoma cells was induced or increased in titre in approximately half of the patient studied. Continued **vaccination** was associated in a number of patients with a decreased LDA titres. Studies on a small samples of patients revealed that this was associated with the development of serum factors which inhibited LDA activity. LDA activity appeared directed to non-**MHC antigens** on melanoma cells which were of at least two specificities. One specificity which was shared with antigens on a number of nonmelanoma carcinoma cells was removed by absorption on fetal brain and may be similar to oncofetal antigens described by other workers. Reactivity against melanocytes was induced in some patients and may underlie the development of vitiligo in several patients. These results suggest that **vaccines** prepared from VMCL may be a favourable method for increasing immune responses against melanoma.

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=> d his


     (FILE 'HOME' ENTERED AT 14:32:18 ON 23 MAR 1998)

     FILE 'MEDLINE, EMBASE, SCISEARCH, CANCERLIT' ENTERED AT 14:33:03 ON
     23 MAR 1998
L1          4371 S MHC ANTIGEN!
L2            86 S VACCIN? AND L1
L3            13 S L2 AND (TUMO!R OR CANCER)
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